REMARKS

The amendments to the specification are made to correct typographical errors made by the European attorney preparing the application that were obviously overlooked by the inventors reviewing it. Specifically, in claim 6 and at several locations in the specification (see Table below), Applicants have referred to stimulating cells with, or using a proliferating agent, that is "CD3/CD28." It is evident to those skilled in the art, and set forth explicitly in multiple other locations in the specification, that one is not using a CD3 or CD28 protein as the mitogen or proliferating agent (for example, as stated at page 15, line 34), but rather, is using a mAb specific for these cell surface proteins. At one location (page 39, line 13; see also Table below), the letter "A" was inadvertently used instead of "α", the use of which is explained below.

Indeed, it is stated in the description of Example I (page 26, lines 7-9) and Example 2 (page 35, lines 21-23) that anti-CD3 and anti CD28 monoclonal antibodies are being used and, moreover, that "α"is being used as an abbreviation for "anti". Applicants have thus decided to amend the specification as indicated above (see Table below for locations in context). In some cases, for maximal clarity, the specification (and claim 6) have been amended to read "anti-CD3 antibody (or antibodies) and anti-CD28 antibody (or antibodies). In several locations, the shorter form of αCD3/CD28 has been used – to remain more consistent with the usage in neighboring passages of the specification. In every case, it should be evident that what is meant is anti-CD3 and anti-CD28 antibodies. These amendments do not add new matter to the specification and their entry is requested.

CLAIMS

Claims 1- 17 and 20-23 remain pending in the application. All of the original claims have been amended. Claims 18 and 19 have been cancelled. New claims 20-23 have been added. The foregoing amendments to the claims have been made to remove multiple dependencies and add new singly dependent claims in place of some formerly multiply dependent claims, *etc.*

Support for the language of amended claim 1

> ...wherein, if the cells comprise lymphocytes, the lymphocytes are not selected or enriched on the basis of their antigen specificity.

is found, *e.g.*, at page 17, lines 5-7, where it is stated that the mononuclear cells are polyclonal and not specific for a predetermined antigen.

Table: Listing of Reference to CD3/CD28 in the Specification

Page #	Line(s)	Original language in specification	Amend?
15	33	proliferating agents include *e.g.* CD3/CD28, IL-2, PHA,	**Amend**
16	28	proliferating agent such as phytohemagglutinin (PHA), or αCD3/CD28	
17	1	CD3/CD28, PHA and/or IL-2.	**Amend**
22	19	stimulated with αCD3/CD28 and IFN-γ and TNF-α	
23	5	(Fig 11) αCD3/CD28 mAbs	
23	14	(Fig. 12) αCD3/CD28 stimulation	
23	21	(Fig 13) αCD3/CD28 mAbs	
23	24	(Fig 13) αCD3/CD28 activated $CD4^+$ cells	
26	7-9	Cells were activated for 24 h with immobilised **anti-(α)** CD3 ...and soluble αCD28 **monoclonal antibodies (mAb)** ...	
27	31	In the presence of *α*CD3/CD28 mAbs	
29	28	...CD3/CD28 activated splenocytes	**Amend**
30	11	In the absence or presence of αCD3/CD28 activation	
32	14	stimulated with αCD3/CD28 mAb	
35	21-23	immobilised anti-(α)CD3 (clone SPV-T3b)[53] and 2 μg/ml soluble *α*CD28 monoclonal antibodies (mAb) ...	
35	31	stimulated for 24 h with αCD3/CD28 as described above	
36	10-11	αCD3/CD28 activated $CD4^+$ cells	
36	21-22	after 48 h of αCD3/CD28 stimulation	
39	5	αCD3/CD28 activated IL-10-GFP $CD4^+$ cells	
39	8	reactivated by CD3/CD28 engagement **	
39	9	after αCD3/CD28 stimulation	
39	13	**A**CD3/CD28 stimulation of control GFP $CD4^+$ cells	**Amend**
39	19	after αCD3/CD28 stimulation	
39	30-31	after 48 hours of αCD3/CD28 activation.	
40	1	72 hours of αCD3/CD28 activation	
40	14	after 48 h of αCD3/CD28 stimulation	
Claim 6		...at least one of CD3/CD28...	**Amend**

**** here the text refers to engagement of the CD3 and CD28 molecules themselves (by the anti-CD3 and anti-CD28 mabs), so it is accurate to omit the "α" or "anti" before "CD3"**

As is known in the art, of the several populations of cells found in a mononuclear cell preparation as described, the only cells that have antigen specificity are lymphocytes, namely, T and B cells. This statement thus teaches that in a preferred embodiment of the invention, there is no advance selection or enrichment of cells (*i.e.*, lymphocytes) on the basis of their antigen specificity. Furthermore, in the description of the Examples of how IL-10 transduced cells were prepared, it is indicated that the investigators started with a population of normal mouse spleen cells (Example 1 – pg 26 line 1) that, by definition, are not selected according to antigen-specificity. These cells were enriched for T cells and dividing cells (using anti-CD3/CD28 mAbs as proliferative stimuli and , IL2 in the medium, etc. In some cases IL-10 expressing cells were further enriched(by sorting for a linked marker, GFP. Example 2 describes use of human peripheral blood mononuclear cells as the starting population. Of these, T cells were first stimulated to proliferate and then transduced with IL-10, after which a subpopulation of CD4+ T cells was enriched. Expression of IL-10 was measured in these selected populations. Again, there was no selection based on antigen-specificity. Thus on the basis of the specification and what is well-known in the art, the amended language of claim 1 is fully supported.

Support for the amendment to claim 6 to recite anti-CD3 and anti-CD28 antibodies is found throughout the specification and in the amendments thereto, as discussed above in detail.

Many of the foregoing amendments to the claims have been made to remove multiple dependencies and add new singly dependent claims in place of some formerly multiply dependent claims, or two split certain claims apart. Two claims were cancelled. Support for the new claims can be found in the original claims, at minimum. Additional amendments are intended to improve the clarity and definiteness of the claim language. No new matter has been added by these amendments. Applicants request that these amendments be entered. The application is now in condition for examination.

If these papers are not considered timely filed by the Patent and Trademark Office, then a petition is hereby made under 37 C.F.R. § 1.136, and any additional fees required under 37 C.F.R. § 1.136 for any necessary extension of time, or any other fees required to complete the filing of this response, may be charged to Deposit Account No. 50-0911. Please credit any overpayment to deposit Account No. 50-0911.

Respectfully submitted,

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By_____

Shmuel Livnat
Registration No.: 33,949
MCKENNA LONG & ALDRIDGE LLP
1900 K Street, N.W.
Washington, DC 20006

Attorneys for Applicant